

WHAT IS CLAIMED IS:

1. A method for treating a malignancy in a subject, comprising administering a pharmaceutically effective amount of a therapeutic agent to the subject, said therapeutic agent comprising an oligosaccharide, wherein said oligosaccharide is heparin or heparan-sulfate derived.

2. The method of claim 1, wherein said oligosaccharide is at least one of carboxylated and sulfated.

3. The method of claim 2, wherein said oligosaccharide is a glucosamine derivative and pharmaceutically acceptable salts thereof.

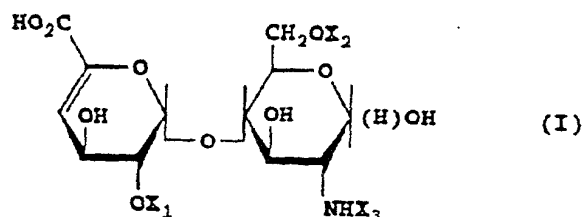
4. The method of claim 3, wherein said derivative is sulfated.

5. The method of claim 4, wherein said oligosaccharide is an N-sulfated 4-deoxy-4-en-iduronoglucosamine having at least one other sulfate group and pharmaceutically acceptable salts thereof.

6. The method of claim 4, wherein said oligosaccharide is an N-acetylated 4-deoxy-4-en-iduronoglucosamine having at least two sulfate groups and pharmaceutically acceptable salts thereof.

7. The method of claim 4, wherein said oligosaccharide is a

disaccharide of formula (I) or its pharmaceutically acceptable salt:



in which X_1 is hydrogen or sulfate; X_2 is hydrogen or sulfate; and X_3 is sulfate or acetyl, provided that if X_3 is sulfate, then at least one of X_1 or X_2 is sulfate and if X_3 is acetyl, then both X_1 and X_2 are sulfates.

7. The method of claim 4, wherein said oligosaccharide is an N-sulfated 4-deoxy-4-en-glucuronoglucosamine having at least one other sulfate group or a pharmaceutically acceptable salt thereof.

8. The method of claim 4, wherein said oligosaccharide is an N-acetylated 4-deoxy-4-en-glucuronoglucosamine having at least two other sulfate groups or a pharmaceutically acceptable salt thereof.

9. The method of claim 1, wherein said oligosaccharide is a sulfated disaccharide.

10. The method of claim 1, wherein said oligosaccharide comprises at least one of DS Po912, DS 1145, DS 1020, DS 8767, DS Po821, DS 9267, DS 9517 and DS 0895.

11. The method of claim 10, wherein said oligosaccharide comprises DS Po912.

12. The method of claim 10, wherein said oligosaccharide is DS 1145.

13. The method of claim 1, wherein the malignancy is a metastatic tumor.

14. The method of claim 13, wherein said metastatic tumor is selected from the group consisting of breast cancer, lung cancer, bone cancer, bladder cancer, rhabdomyosarcoma, angiosarcoma, adenocarcinoma, prostate cancer, colon cancer, squamous cell carcinoma of the cervix, ovarian cancer, malignant fibrous histiocyte, skin cancer, leiomyosarcoma, astrocytoma, glioma and hepatocellular carcinoma.

15. The method of claim 14, wherein the malignancy is lung cancer.

16. The method of claim 1, wherein said oligosaccharide is administered

in an amount in a range of from about 1 to about 1000 micrograms of oligosaccharide per Kg of subject, weight per weight.

17. A method for treating a metastatic cancer in a subject, comprising administering a pharmaceutically effective amount of a therapeutic agent to the subject, said therapeutic agent comprising an oligosaccharide, wherein said oligosaccharide is at least one of carboxylated and sulfated.

18. The method of claim 17, wherein said oligosaccharide is a glucosamine derivative and pharmaceutically acceptable salts thereof.

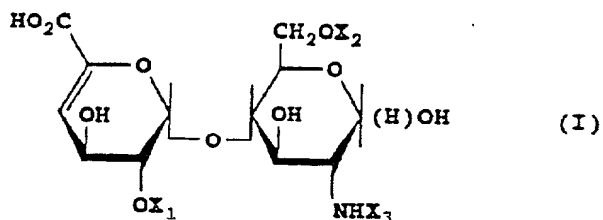
19. The method of claim 18, wherein said derivative is sulfated.

20. The method of claim 19, wherein said oligosaccharide is a sulfated disaccharide.

21. The method of claim 20, wherein said oligosaccharide is an N-sulfated 4-deoxy-4-en-iduronoglucosamine having at least one other sulfate group and pharmaceutically acceptable salts thereof.

22. The method of claim 20, wherein said oligosaccharide is an N-acetylated 4-deoxy-4-en-iduronoglucosamine having at least two sulfate groups and pharmaceutically acceptable salts thereof.

23. The method of claim 20, wherein said oligosaccharide is a disaccharide of formula (I) or its pharmaceutically acceptable salt:



in which X_1 is hydrogen or sulfate; X_2 is hydrogen or sulfate; and X_3 is sulfate or acetyl, provided that if X_3 is sulfate, then at least one of X_1 or X_2 is sulfate and if X_3 is acetyl, then both X_1 and X_2 are sulfates.

24. The method of claim 20, wherein said oligosaccharide is an N-sulfated 4-deoxy-4-en-glucuronoglucosamine having at least one other sulfate group or a pharmaceutically acceptable salt thereof.

25. The method of claim 20, wherein said oligosaccharide is an N-acetylated 4-deoxy-4-en-glucuronoglucosamine having at least two other sulfate groups or a pharmaceutically acceptable salt thereof.

26. The method of claim 17, wherein said oligosaccharide comprises at

least one of DS Po912, DS 1145, DS 1020, DS 8767, DS Po821, DS 9267, DS 9517 and DS 0895.

27. The method of claim 26, wherein said oligosaccharide comprises DS Po912.

28. The method of claim 26, wherein said oligosaccharide is DS 1145.

29. The method of claim 17, wherein said oligosaccharide alters localization of tumor cells to treat the metastatic cancer.

30. The method of claim 17, wherein said oligosaccharide alters homing activity of tumor cells to treat the metastatic cancer.

31. The method of claim 17, wherein said oligosaccharide interferes with the CXCR4 7TM-GPCR signaling pathway.

References

1. Muller, A., B. Homey, H. Soto, N. Ge, D. Catron, M. E. Buchanan, T. McClanahan, E. Murphy, W. Yuan, S. N. Wagner, J. L. Barrera, A. Mohar, E. Verastegui, and A. Zlotnik. 2001. Involvement of chemokine receptors in breast cancer metastasis. *Nature* 410:50.
2. Sehgal, A., S. Ricks, A. L. Boynton, J. Warrick, and G. P. Murphy. 1998. Molecular characterization of CXCR-4: a potential brain tumor- associated gene. *J Surg Oncol* 69:239.
3. Sehgal, A., C. Keener, A. L. Boynton, J. Warrick, and G. P. Murphy. 1998. CXCR-4, a chemokine receptor, is overexpressed in and required for proliferation of glioblastoma tumor cells. *J Surg Oncol* 69:99.
4. Rossi, D., and A. Zlotnik. 2000. The biology of chemokines and their receptors. *Annu Rev Immunol* 18:217.
5. Braun, S. E., K. Chen, R. G. Foster, C. H. Kim, R. Hromas, M. H. Kaplan, H. E. Broxmeyer, and K. Cornetta. 2000. The CC chemokine CK beta-11/MIP-3 beta/ELC/Exodus 3 mediates tumor rejection of murine breast cancer cells through NK cells. *J Immunol* 164:4025.
6. Bleul, C. C., M. Farzan, H. Choe, C. Parolin, I. Clark-Lewis, S. J., and T. A. Springer. 1996. The lymphocyte chemoattractant SDF-1 is a ligand for LESTR/fusin and blocks HIV entry. *Nature* 382:829.
7. Murdoch, C., and A. Finn. 2000. Chemokine receptors and their role in inflammation and infectious diseases. *Blood* 95:3032.

8. Oberlin, E., A. Amara, F. Bachelierie, C. Bessia, J. Virelizier, F. Arenzana-Seisdedos, O. Schwartz, J. Heard, I. Clark-Lewis, D. F. Legler, M. Loetscher, M. Baggiolini, and B. Moser. 1996. The CXC chemokine SDF-1 is the ligand for LESTR/fusin and prevents infection by T-cell-line-adapted HIV-1. *Nature* 382:833.
9. Nagasawa, T., S. Hirota, K. Tachibana, N. Takakura, S. Nishikawa, Y. Kitamura, N. Yoshida, H. Kikutani, and T. Kishimoto. 1996. Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. *Nature* 382:635.
10. McGrath, K. E., A. D. Koniski, K. M. Maltby, J. K. McGann, and J. Palis. 1999. Embryonic expression and function of the chemokine SDF-1 and its receptor, CXCR4. *Dev Biol* 213:442.
11. Ponomaryov, T., **A. Peled**, I. Petit, R. S. Taichman, L. Habler, J. Sandbank, F. Arenzana-Seisdedos, A. Magerus, A. Caruz, N. Fujii, A. Nagler, M. Lahav, M. Szyper-Kravitz, D. Zipori, and T. Lapidot. 2000. Induction of the chemokine stromal-derived factor-1 following DNA damage improves human stem cell function [In Process Citation]. *J Clin Invest* 106:1331.
12. Gonzalo, J. A., C. M. Lloyd, **A. Peled**, T. Delaney, A. J. Coyle, and J. C. Gutierrez-Ramos. 2000. Critical involvement of the chemotactic axis CXCR4/stromal cell-derived factor-1 alpha in the inflammatory component of allergic airway disease. *J Immunol* 165:499.
13. **Peled, A.**, V. Grabovsky, L. Habler, J. Sandbank, F. Arenzana-Seisdedos, I. Petit, H. Ben-Hur, T. Lapidot, and R. Alon. 1999. The chemokine

SDF-1 stimulates integrin-mediated arrest of CD34(+) cells on vascular endothelium under shear flow. *J Clin Invest* 104:1199.

14. **Peled, A.,** I. Petit, O. Kollet, M. Magid, T. Ponomaryov, T. Byk, A. Nagler, H. Ben-Hur, A. Many, L. Shultz, O. Lider, R. Alon, D. Zipori, and T. Lapidot. 1999. Dependence of human stem cell engraftment and repopulation of NOD/SCID mice on CXCR4. *Science* 283:845.

15. Sawada, S., K. Gowrishankar, R. Kitamura, M. Suzuki, G. Suzuki, S. Tahara, and A. Koito. 1998. Disturbed CD4+ T cell homeostasis and in vitro HIV-1 susceptibility in transgenic mice expressing T cell line-tropic HIV-1 receptors. *J. Exp. Med.* 187:1439.

16. Aiuti, A., I. J. Webb, C. Bleul, T. Springer, and J. C. Gutierrez-Ramos. 1997. The chemokine SDF-1 is a chemoattractant for human CD34+ hematopoietic progenitor cells and provides a new mechanism to explain the mobilization of CD34+ progenitors to peripheral blood. *J Exp Med* 185:111.

17. **Peled, A.,** O. Kollet, T. Ponomaryov, I. Petit, S. Franitza, V. Grabovsky, M. Magid Slav, A. Nagler, O. Lider, A. R., D. Zipori, and T. Lapidot. 2000. The chemokine SDF-1 activates the integrins LFA-1, VLA-4 and VLA-5 on immature human CD34+ cells: role in transendothelial/stromal migration and engraftment of NOD/SCID Mice. *Blood* 95:3289.

18. Edinger, M., T. J. Sweeney, A. A. Tucker, A. B. Olomu, R. S. Negrin, and C. H. Contag. 1999. Noninvasive assessment of tumor cell proliferation in animal models. *Neoplasia* 1:303.

19. Contag, P. R., I. N. Olomu, D. K. Stevenson, and C. H. Contag.

[illegible]

- Contag. 1999. Bioluminescence for biological sensing in living mammals. *Adv Exp Med Biol* 471:775.

21. Condiotti, R., and A. Nagler. 1998. Effect of interleukin-12 on antitumor activity of human umbilical cord blood and bone marrow cytotoxic cells. *Exp Hematol* 26:571.

22. Naldini, L. 1999. In vivo gene delivery by lentiviral vectors. *Thromb Haemost* 82:552.